Acute hemodynamic changes by breathing hypoxic and hyperoxic gas mixtures in pulmonary arterial and chronic thromboembolic pulmonary hypertension

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Abstract: BACKGROUND There is insufficient evidence to counsel patients with pulmonary hypertension undergoing altitude or air travel. We thus aimed to study hemodynamic response of patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH) during changes in inspiratory oxygen partial pressure. METHODS AND RESULTS Consecutive patients undergoing right heart catheterization had hemodynamic assessments whilst breathing ambient air (normoxia, FiO 0.21, at altitude 490 m), nitrogen-enriched air (hypoxia, FiO 0.16, simulated altitude 2600 m) and oxygen (hyperoxia, FiO 1.0), each for 10 min. Data from patients with PAH/CTEPH with mean pulmonary artery pressure (mPAP) 25 mmHg, pulmonary artery wedge pressure 15 mmHg, were compared to data from controls, mPAP <20 mmHg. 28 PAH/CTEPH-patients, 15 women, median age (quartiles) 62y (49;73), mPAP 35 mmHg (31;44), PaO 7.1 kPa (6.8;9.3) and 16 controls, 12 women, 60y (52;69), mPAP 18 mmHg (16;18), PaO 9.5 kPa (8.5;10.6) were included. Hypoxia reduced the PaO in PAH/CTEPH-patients by median of 2.3 kPa, in controls by 3.3 kPa, difference (95%CI) in change 1.0 (0.02 to 1.9), $p < 0.05$. Corresponding changes in pulmonary vascular resistance, mPAP and cardiac output were non-significant in both groups. Hyperoxia decreased mPAP in PAH/CTEPH-patients by 4 mmHg (2 to 6), in controls by 2 mmHg (0 to 3), difference in change 3 mmHg (0 to 5), $p < 0.05$. CONCLUSIONS In patients with PAH/CTEPH, very short-term exposure to moderate hypoxia similar to 2600 m altitude or during commercial air travel did not deteriorate hemodynamics. These results encourage studying the response of PAH/CTEPH during daytrips to the mountain or air travel.

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All author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Abstract

Background

There is insufficient evidence to counsel patients with pulmonary hypertension undergoing altitude or air travel. We thus aimed to study hemodynamic response of patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH) during changes in inspiratory oxygen partial pressure.

Methods and Results

Consecutive patients undergoing right heart catheterization had hemodynamic assessments while breathing ambient air (normoxia, FiO_2 0.21, at altitude 490m), nitrogen-enriched air (hypoxia, FiO_2 0.16, simulated altitude 2600m) and oxygen (hyperoxia, FiO_2 1.0), each for 10 min. Data from patients with PAH/CTEPH with mean pulmonary artery pressure (mPAP) ≥25mmHg, pulmonary artery wedge pressure ≤15mmHg, were compared to data from controls, mPAP <20mmHg.

28 PAH/CTEPH-patients, 15 women, median age (quartiles) 62y (49;73), mPAP 35mmHg (31;44), PaO_2 7.1kPa (6.8;9.3) and 16 controls, 12 women, 60y (52;69), mPAP 18mmHg (16;18), PaO_2 9.5kPa (8.5;10.6) were included. Hypoxia reduced the PaO_2 in PAH/CTEPH-patients by median of 2.3kPa, in controls by 3.3kPa, difference (95%CI) in change 1.0 (0.02 to 1.9), $P<0.05$. Corresponding changes in pulmonary vascular resistance, mPAP and cardiac output were nonsignificant in both groups. Hyperoxia decreased mPAP in PAH/CTEPH-patients by 4mmHg (2 to 6), in controls by 2mmHg (0 to 3), difference in change 3mmHg (0 to 5), $P<0.05$.

Conclusions

In patients with PAH/CTEPH, very short-term exposure to moderate hypoxia similar to 2600m altitude or during commercial air travel did not deteriorate hemodynamics. These results encourage studying the response of PAH/CTEPH during daytrips to the mountain or air travel.

Introduction

Worldwide, millions of people are travelling to mountain areas or undergo air travel exposing themselves to hypobaric hypoxia. In healthy individuals, moderate hypoxia induces an elevation of pulmonary artery pressure (PAP) that is generally well tolerated. In patients with preexisting pulmonary hypertension (PH) there have been concerns that exposure to even mild hypoxia might induce an excessive further rise in PAP leading to a clinically relevant hemodynamic decompensation with dyspnea, risk of syncope and right heart failure although this has not been conclusively studied. According to current guidelines, patients with PH in NYHA functional classes III/IV and/or PaO_2 ≤60mmHg (≤8 kPa) at sea level should avoid altitudes above 2000 m without supplemental oxygen, but this recommendation is based on expert opinion in lack of studies. [1] Some experts recommend to perform a hypoxia simulation test to counsel patients with respiratory conditions with an oxygen saturation <95% at sea level for fitness for flight. [2] However, the contribution of such testing in preventing adverse events during air travel or altitude exposure has not been validated [3, 4].

Pulmonary vascular remodeling is one of the hallmarks of PH that results in increased pulmonary vascular resistance (PVR) and, hence, elevated PAP. PH is associated with arterial hypoxemia, especially during exercise, due to a decreased cardiac output (CO) with low mixed venous oxygen saturation ($SmvO_2$) and inefficiency of pulmonary gas exchange. PH-associated hypoxemia may be a major contributor to a vicious cycle of hypoxic pulmonary vasoconstriction (HPV) [5] that promotes endothelial dysfunction and further worsening of pulmonary hemodynamics. [6] HPV is defined as a homeostatic mechanism triggered via hypoxia, where pulmonary arteries constrict to optimate the ventilation/perfusion matching as well as the systemic oxygen delivery. [7] Unfortunately, data on the acute effects of exposure to hypoxia in patients with PH are scant. It is therefore difficult to counsel PH patients wishing to undergo mountain or air travel.

To address this point, the current study was designed to quantify the hemodynamic response to an exposure to moderate hypoxia similar to that encountered during commercial air travel or at moderate altitude in patients with precapillary PH. We tested the hypothesis that hypoxia would induce a further rise in mPAP or PVR in these patients. In addition, we intended to evaluate potential predictors of an excessive rise in mPAP and PVR during exposure to hypoxia. Since equipment for hypoxic testing is not widely available we investigated whether a pronounced pulmonary vasoreactivity to hyperoxia, i.e., 100%

oxygen breathing that can be more conveniently applied than hypoxia, would identify PH patients with a marked response to hypoxia.

Methods

Study design and participants

This case control study compared acute hemodynamic effects of breathing hypoxic air and oxygen in patients with PAH/CTEPH and dyspneic controls without PH undergoing RHC at the PH-Center, University Hospital Zurich (altitude 490 m, mean barometric pressure 730 mmHg).

Patients were included if they were diagnosed with PAH or CTEPH according to guidelines if mPAP was ≥25 mmHg and pulmonary artery wedge pressure (PAWP) ≤15 mmHg. [8] Patients were excluded if they were severely hypoxemic (PaO_2 ≤7.3 kPa) under ambient air, had PAWP >15mmHg, relevant lung disease (FEV_1 or FVC < 60%), i.e. PH groups other than I and IV. [9] Controls were dyspneic patients undergoing RHC with a mPAP <20 mmHg and PAWP <15 mmHg. [1]

Participants gave written informed consent for RHC and have their data registered. The study was approved by the local ethics committee (KEK: 2016-02136) and registered (clinicaltrials.gov, NCT03195959).

Interventions and assessments

Supine RHC was performed from a jugular venous access using a balloon-tipped, triple-lumen, fluid-filled 7.5F Swan-Ganz catheter and Edwards Vigilance Monitor for CO-measurements by thermodilution. Zero reference was set at the level of the left atrium in mid-axillary line. [10, 11] Baseline measurements were obtained during stable conditions at rest on ambient air (FiO_2 0.21). Subsequently, patients were exposed to hypoxia (FiO_2 0.16, altitude equivalent 2600 m) via a tight-fitting mouthpiece simulated by a SMTEC AltiTrainer for 10 minutes. [12] Following a 10-minute wash-out period, patients were exposed to hyperoxia (oxygen breathing, FiO_2 1.0) for 10 minutes, administered via a non-rebreathing valve from a reservoir bag (AmbuSPUR II, Synmedic AG). The following hemodynamics were assessed at baseline and at the end of hypoxia/hyperoxia: heart rate (HR), systolic, mean and diastolic systemic blood pressure (sSBP, mSBP, dSBP), systolic, mean and diastolic PAP (sPAP, mPAP, dPAP), PAWP and right atrial pressure. Cardiac index (CI) was calculated as CO/body surface area. PVR was calculated as (mPAP-PAWP)/CO and SVR as (mSBP-right atrial pressure)/CO. The alveolar-arterial PO_2 gradient was calculated as: $(FiO_2*(PAtm - PH_2O)) - (PaCO_2/RER)+(PaCO_2* FiO_2*(1- RER)/RER)-PaO_2$, where PAtm is barometric pressure and RER respiratory exchange ratio (assumed to be 0.8). Arterial and mixed-venous

oxygen saturations (SaO_2/$SmvO_2$) were measured from respective radial/pulmonary artery samples. Arterial and mixed venous oxygen content were calculated as (1.34*hemoglobin concentration *SaO_2 [or $SmvO_2$])+(0.0031*PaO_2 [or $PmvO_2$]). Oxygen delivery and oxygen consumption were computed as CO*arterial oxygen content and CO*(arterial – mixed-venous oxygen content), respectively. The hypoxic and hyperoxic pulmonary vascular reactivity was quantified by calculating changes in mPAP divided by corresponding changes in PaO_2 induced by hypoxia and hyperoxia (ΔmPAP/ΔPaO_2); the ventilatory response to hypoxia and hyperoxia was quantified by calculating changes in $PaCO_2$ divided by corresponding changes in PaO_2 induced by hypoxia and hyperoxia ($\Delta PaCO_2/\Delta PaO_2$).

The 6-minute walk distance (6MWD), NYHA-functional class, NT-pro-brain natriuretic peptide and demographics were assessed within 2 days of RHC.

Statistical analysis

Normality of distribution was tested by the Shapiro-Wilk test. Variables were summarized as median (quartiles) and changes as median (95% confidence interval). Wilcoxon matched pairs tests were used as appropriate. Regression analyses were performed to assess responses after adjusting for baseline values and to evaluate whether the response to hyperoxia predicted the response to hypoxia. A two-sided p-value <0.05 was considered significant. IBM SPSS Statistics 23 was used.

Results

The patient flow is shown in figure 1. From the 44 participants 28 (64%) had PAH/CTEPH, 16 (36%) were controls (table 1). The majority of patients were in NYHA functional class II/III (77%). Resting SpO_2, 6MWD and SpO_2 at the end of the 6MWD were similar in PH and controls, whereas NT-pro-BNP and mPAP were higher in PH-patients. Of the 28 PH-patients, 5 were treated with PH-specific drugs (table 1).

Assessments during exposure to hypoxia

Exposure to hypoxia was well tolerated by patients and controls without any discomfort or adverse events. Hemodynamic and blood oxygenation variables under normoxia and hypoxia are numerically summarized in table S1 (see supplement) and graphically illustrated in figure 2. Hypoxia significantly reduced PaO_2 and SpO_2 in both groups but to a greater extent in controls than in patients with

PAH/CTEPH. This was associated with an increased HR but no change in mPAP, mSBP and CO in any of the 2 groups. There was a minimal increase in PVR related to a slight reduction in PAWP in controls. As there was no significant change in mPAP, the measure of vascular reactivity to hypoxia ($\Delta mPAP/\Delta PaO_2$) was small and similar in both groups. In PAH/CTEPH, there was a significant decrease in arterial oxygen content, oxygen delivery and oxygen consumption during hypoxia but these changes were not statistically different from those in controls. Hypoxia induced a respiratory alkalosis in PAH/CTEPH but not in controls although the difference in pH and $PaCO_2$ changes were not statistically significant. There was a small but significant difference in the measure of ventilatory response to hypoxia ($\Delta PaCO_2/\Delta PaO_2$) between the two groups indicating a higher hyperventilatory response in PAH/CTEPH.

Assessments during exposure to hyperoxia

Hemodynamics and blood oxygenation variables under normoxia and hyperoxia are numerically summarized in table S2 (see supplement) and graphically illustrated in figure 2. Under hyperoxia, there was a major increase in PaO_2, SaO_2 $SmvO_2$ and a decrease in the HR in both groups. There was no change in mSBP but the mPAP significantly decreased in PAH/CTEPH patients but this was not associated with a significant decrease in PVR. Hyperoxia induced minor decreases in CI and in oxygen delivery that were statistically significant in controls only. The measure of pulmonary vascular reactivity to hyperoxia ($\Delta mPAP/\Delta PaO_2$) was significantly greater in PAH/CTEPH than in control. Despite major changes in PaO_2, the changes in $PaCO_2$ were minimal in both groups.

Multiple regression to predict the hypoxia-induced change in PVR

Multivariate regression analysis revealed no correlation of the changed in PVR induced by hypoxia with any of the measured parameters (table S3).

To evaluate whether changes in mPAP respectively PVR during exposure to hypoxia could be predicted by the response to hyperoxia multiple regression analysis was performed with change in mPAP respectively PVR during hypoxia as dependent variable and sex, age, baseline mPAP respectively PVR, baseline PaO_2, and change in mPAP respectively PVR in response to hyperoxia as independent variables. This analysis revealed that the change in mPAP respectively PVR could be predicted by the change in mPAP respectively PVR under hyperoxia (table 2a and b)

Discussion

This study investigated acute effects of normobaric hypoxia and hyperoxia on invasively measured pulmonary hemodynamics and blood oxygenation in patients with PAH/CTEPH in comparison to controls without PH. Our results demonstrate that a degree of hypoxia corresponding to that encountered during commercial air travel or ascent to an altitude of 2600 m was well tolerated at short time by PAH/CTEPH patients and controls alike without significant changes in mPAP, PVR or CO although hypoxia induced a slight decrease in oxygen delivery. The lack of hemodynamic deterioration during exposure to mild hypoxia is encouraging to further investigate PAH/CTEPH patients during daytrips to altitude or air travel. During hyperoxia, PAH/CTEPH patients revealed a significant decrease in mPAP suggesting that pulmonary vasoreactivity to hyperoxia was maintained consistent with results from our previous studies demonstrating a beneficial effect of supplemental oxygen on exercise performance in PAH/CTEPH patients. [12, 13] Of interest, the change in mPAP respectively PVR under hypoxia could be predicted by the change in mPAP respectively PVR under hyperoxia, suggesting that this relatively simple vasoreactivity test deserves evaluation as risk assessment tool for PAH/CTEPH planning altitude exposure or air travel.

HPV is an important mechanism supporting ventilation-perfusion matching in the lung, redirecting blood flow from hypoxic to oxygen-rich areas. However, in healthy individuals exposed to a hypoxic environment HPV leads to an increase in mPAP in relation to the degree of hypoxia. [14, 15] T [16]. [17] The HPV arises immediately after exposure to hypoxia. [18] In the current study, acute hypoxia did not change the mPAP, PVR nor CO in PAH/CTEPH patients and controls. The absence of a significant response in these variables may be related to the relatively minor degree of hypoxia corresponding to an altitude of 2600 m that only increased HR but did not induce further changes in hemodynamics. In PAH/CTEPH patients, mechanisms preventing further HPV in the remodeled pulmonary arteries and adaptation of the right ventricle to a chronically elevated afterload might have contributed to the lack of significant hemodynamic changes during exposure to hypoxia other than a mild HR elevation. The elevated HR is consistent with some previous data in patients with PAH [19-21] and with studies in healthy individuals upon acute exposure to altitude and consistent with activation of carotid and aortic chemoreceptors and a decrease in arterial baroreflex activation. [22] However, despite this HR-increase, we could not demonstrate a change in cardiac output under hypoxia and which implies a certain decrease

in stroke volume in our collective. The hyperoxia-induced HR-reduction may be beneficial in PH patients [23], since tachycardia in PH is associated with worse outcome [12, 24] and supports treatment with supplemental oxygen in hypoxemic patients.

Hypoxia induced a marked hyperventilation in patients with PAH/CTEPH reflected by a decreased $PaCO_2$, whereas no significant change in $PaCO_2$ was observed in controls. The pronounced hyperventilatory response to hypoxia in PAH/CTEPH patients was likely related to sympathetic overexcitation associated with elevated chemosensitivity. Correspondingly, in PAH/CTEPH patients with exercise-induced hypoxemia we previously observed a pronounced hyperventilation during exercise with high ventilatory equivalents for CO_2 output and elevated HR, responses that were reduced by breathing hyperoxic air. [12]

Breathing of oxygen (hyperoxia) induced a significant decrease of mPAP in PAH/CTEPH patients, whilst there was no such change in the control group. Accordingly, the measure of the pulmonary vascular reactivity to hyperoxia ($\Delta mPAP/\Delta PaO_2$) was higher in PAH/CTEPH compared to controls. The reduction in PVR associated with the decrease in mPAP during hyperoxia in PAH/CTEPH patients was not quite statistically significant ($p=0.059$) since the heart rate and cardiac output were reduced as well. The findings may suggest that despite longstanding PH and, presumably, pulmonary vascular remodeling some degree of vascular reactivity to changes in alveolar PO_2 was maintained, which is consistent with improvement of hemodynamics and physical performance of PAH/CTEPH patients by oxygen therapy. [25]. [12, 23, 26] . [17]

In previous observational studies in PH patients [27-29] moderate hypoxia induced by travelling in airplanes with cabins pressurized to an altitude equivalent of ~2000 m was well tolerated. As some patients revealed symptomatic hypoxemia during air-travel it seems nevertheless advisable to offer supplemental oxygen therapy during flights at least in patients with low resting PaO_2 or exercise-induced hypoxemia at sea level, although there is no conclusive evidence to support this. However, the predictive value of hypoxia testing in respiratory patients has not been shown [3, 4]. However, as we could show that the change in mPAP respectively PVR induced by hypoxia could be predicted by the acute vasoreactivity to hyperoxia, it might be worth to evaluate hyperoxia testing as simple predictive tool to counsel PAH/CTEPH-patients undergoing altitude sojourns or air travel. Whether such kind of risk assessment might be of value and whether it could be done non-invasively by assessments of changes in

estimated sPAP by transthoracic echocardiography under hyperoxia remains to be studied. Seccombe et al demonstrated that changes in right heart function and sPAP could be non-invasively assessed by echocardiography during short-term exposure to hypoxia [30] and it seems thus reasonable to assume that vasoreactivity testing during simple hyperoxia would be feasible and more widely available for patients with PAH/CTEPH. Our results are in line with earlier studies showing that short-term exposure to hypoxia (FiO2 15%) revealed an only minor average increase in mPAP by 3.2mmHg in 26 patients with chronic bronchitis [31].

A limitation of our study is the fact that the control group did not consist of healthy subjects but of patients with dyspnea undergoing RHC that ruled out PH However, we considered performing RHC in healthy subjects as ethically inacceptable in the current investigation. We also included a relatively small number of PH-patients, which might have reduced the power of the results and we included patients with PAH or CTEPH, However, PH is a rare disease and in this paper, we focused on the vasoreactivity response in PH, which largely is shared in PAH and CTEPH [32]. A 10-min exposure time to hypoxia/hyperoxia is relatively short. Nevertheless, it was sufficiently long to induce significant acute hemodynamic changes. Whether longer exposure to hypoxia would deteriorate pulmonary hemodynamics or whether adaptive mechanisms would prevent adverse changes remains to be clarified in future studies.

Conclusion

Our study shows that short-term exposure to normobaric hypoxia corresponding to an altitude of 2600 m or hypoxemia experience during air travel did not induce hemodynamic deterioration assessed by right heart catheter in patients with PAH/CTEPH. Further studies in patients with PH should focus on safety and tolerability of longer-term exposure to hypoxia during real-life conditions in alpine environments or long-distance air travel in order to create a scientific basis for counselling these increasingly active patients. The change of mPAP respectively PVR under hypoxia could be predicted by respective changes under hyperoxia, which confirms some degree of pulmonary vasoreactivity in PAH/CTEPH patients and is consistent with a beneficial effect of oxygen therapy.

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Figure legends:

Fig. 1 Patient flow

Fig. 2 Synopsis of physiologic changes during hypoxia and hyperoxia compared to normoxia in PH patients and in the control group. The values represent medians.* represents a significant difference ($p<0.05$) within groups during exposure to hypoxia/hyperoxia, # represents a significant difference ($p<0.05$) between both groups.